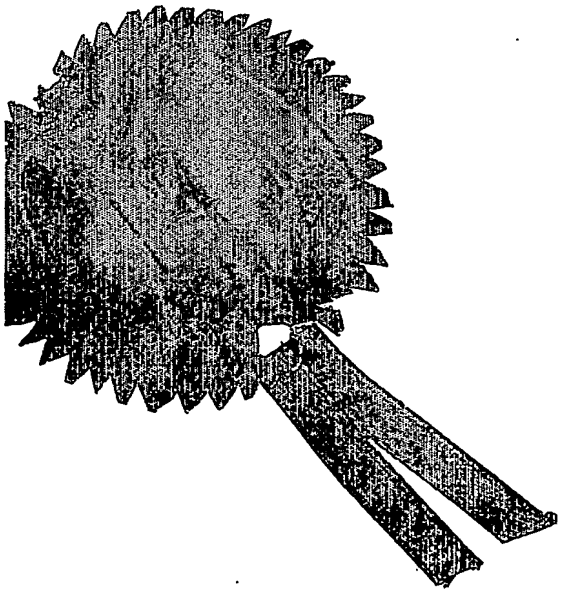
IB/04/03380

सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Provisional Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.* ***1284/Del/2003*** *dated* ***17th October 2003.***



Witness my hand this 1st day of March 2005.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

FORM 1 1284 DEL 03

THE PATENTS ACT, 1970
(39 of 1970)

17 OCT 2003

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PRODUCTION OF TACROLIMUS (FK-506) USING NEW STREPTOMYCES SPECIES"**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are:

a. **PARVEEN KUMAR**
b. **SUNITA SHARMA**
c. **ANIRUDDHA SHUKLA**
d. **SUDEEP KUMAR**
e. **RAJKUMAR MAURYA**
f. **VIKAS KATIAL**
g. **ASHOKE MITRA**
h. **PARESH GIGRAS**

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.
Tel. No. (91-124) 2343126, 2342001–10; 5012501-10

Following declaration was given by the inventors or applicants in the convention country:

We, PARVEEN KUMAR, SUNITA SHARMA, ANIRUDDHA SHUKLA, SUDEEP KUMAR, RAJKUMAR MAURYA, VIKAS KATIAL, ASHOKE MITRA, PARESH GIGRAS of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.
(PARVEEN KUMAR)
b.
(SUNITA SHARMA)
c.
(ANIRUDDHA SHUKLA)
d.
(SUDEEP KUMAR)
e.
(RAJKUMAR MAURYA)
f.
(VIKAS KATIAL)
g.
(ASHOKE MITRA)
h.
(PARESH GIGRAS)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
    a. Provisional Specification (3 copies)
    b. Drawings (3 copies)
    c. Priority document(s)
    d. Statement and Undertaking on FORM – 3
    e. Power of Authority (Not required)
    f. Fee Rs.3,000/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on HDFC Bank, New Delhi.

We request that a patent may be granted to us for the said invention.

Dated this 17TH day of **October, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

1284 DEL 03

FORM 2

The Patents Act, 1970

(39 of 1970)

PROVISIONAL SPECIFICATION

(See Section 10)

PRODUCTION OF TACROLIMUS (FK-506) USING NEW STREPTOMYCES SPECIES

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the production of immunosuppressant agent, tacrolimus (FK-506) utilizing the new microorganism *Streptomyces glaucescens* MTCC 5115.

In the recent past a variety of macrolide compounds have been used as immunosuppressive agents for prevention of graft rejection in bone marrow and organ transplantations and in the treatment of various auto-immune diseases. One widely accepted immunosuppressant for prevention of graft rejection is cyclosporine A, herein onwards referred to as CsA. Although CsA is widely used in immunosuppressive therapy, its usage particularly in higher concentrations is often accompanied by side effects like nephrotoxicity, hepatotoxicity and central nervous system disorders.

In light of this, newer safer drugs exhibiting less side effects and more potency are constantly being searched. As a result, new compounds like rapamycin and its derivative ascomycin or synthetic analogs collectively called as ascomycins have been discovered as immunosuppressants. Among Ascomycins, FK-506, commonly called as tacrolimus of Formula I as shown in the accompanied drawing, has been demonstrated to be potent immunosuppressant.

Furthermore FK-506 and its derivatives have been shown to be effective in treating a number of diseases like Asthma, (PCT Application No. WO 90/14826) inflammatory and hyperproliferative skin disease and cutaneous manifestations of immunologically induced illness (European Patent No. EP 315978). In spite of its extreme usefulness and higher potency for prevention of graft rejection, FK-506 production has its own drawbacks such as low

productivity especially by fermentation due to several related substances being produced during the process.

Various processes for production of FK-506 have been reported in the literature. US Patents 4,894,366; 5,116,756; 5,264,355; 5,496,727 and 5,624,842 cover various strains of Streptomyces species for the production of FK-506.

In order to increase the productivity of FK-506 with simultaneous reduction in the several impurities produced during the process of fermentation, we embarked upon isolating new strain of the *Streptomyces* species capable of producing FK-506. The strain improvement and process optimization involving new technique to have higher productivity of FK-506 with fewer impurities was the objective set to solve the problems associated with prior-art.

It has been found that the immunosuppressant, FK-506 (FR-900506), can be obtained by the fermentation of the microorganism *Streptomyces glaucescens* MTCC 5115, under submerged aerobic conditions in an aqueous carbohydrate medium, containing a nitrogen nutrient, and said conditions being conducted at a pH of about 6.8 to 7.5. The produced compound possesses and displays all of the physical and chemical characteristics of FK-506 (FR-900506) as described in EPO Publication No. 0184162.

In accordance with this invention, there is provided a process for producing the immunosuppressant, identified as FK-506, comprising the step of culturing a strain of *Streptomyces glaucescens* MTCC 5115, or mutant thereof, using conventional methods, under

submerged aerobic fermentation conditions in an aqueous carbohydrate medium, containing a nitrogen nutrient, for a sufficient time to produce the product FK-506.

Also provided is the new microorganism, *Streptomyces glaucescens* MTCC 5115 in biologically pure form.

First aspect of the present invention provides a new microorganism, henceforth named *Streptomyces glaucescens* MTCC 5115, which has been isolated from soil samples collected from Narnaul, (Haryana), India.

Second aspect of the present invention provides a new microorganism *Streptomyces glaucescens* MTCC 5115 useful in the production of FK-506.

Third aspect of the present invention provides a new fermentation technique for the increased production of FK-506 using the new microorganism *Streptomyces glaucescens* MTCC 5115 wherein the ratio of FK-506 to impurities or related products is more. This new technique also provides an advantage as all plant derived raw materials are used in this thus it is free from all the Transmissible Spongiform Encephalitis (TSE) / Bovine Spongiform Encephalitis (BSE) issues.

Fourth aspect of the present invention provides a process for the production of FK-506, which comprises fermenting *Streptomyces glaucescens* MTCC 5115 in a suitable medium e.g. a medium containing glucose, dextrin, glycerol, cotton seed meal, soybean meal, soy peptone, calcium carbonate and potassium salts and recovering the FK-506 there from.

Fifth aspect of the present invention provides the fermentation medium which comprises of:

Components	**g/L**
Dextrose	5.0 – 30.0
Dextrin	30 - 200
Cotton seed meal	5.0 – 20.0
Soy bean meal	5.0 – 20.0
Soy peptone	5.0 – 20.0
Glycerol	5.0 – 30.0
KH_2PO_4	0.2 - 1.5
$CaCO_3$	0.5 - 3.0
Polyethylene glycol	1.0 - 10.0

The fermentation is carried out under submerged aerobic conditions at a temperature between about 20°C and 40°C, preferably 24°-35°C, for a period of about 120 hours to 400 hours, which may be varied according to fermentation conditions and scales. Preferably, the production cultures are incubated for about 240 to 310 hours at 27°C at a pH of about 6.8 – 7.5.

The FK-506 can be obtained by culturing the microorganism *Streptomyces glaucescens* MTCC 5115, under submerged aerobic conditions in an aqueous carbohydrate medium, containing nitrogen nutrients and mineral salts.

Even though the first aspect of present invention provides new microorganism for production of FK-506, it is also anticipated that the aspect also includes use of any of its mutants/ variants which are capable of producing FK-506 substance including natural as well as artificial

mutants which can be obtained from the described organism by conventional means such as irradiation by UV, X-rays, gamma rays and treatment with N-Methyl-N'-nitro-N-nitrosoguanidine (NTG), ethyl methanesulphonate (EMS), methyl methanesulphonate (MMS) and the like or genetic manipulations.

Streptomyces glaucescens, isolated from the soil samples collected from Narnaul, Haryana, India, has been deposited under Budapest treaty under accession number MTCC 5115 at Microbial Type Culture Collection (MTCC), Chandigarh, India. The morphological, cultural, biological and physiological characteristics are described herein below.

Morphological & cultural characteristics of *Streptomyces glaucescens* MTCC 5115

Analysis of whole cell hydrolysate of the strain showed the presence of LL-diaminopimelic acid. Accordingly, the cell wall of this strain is believed to be of type-I (Becker, B. et al., Applied Microbiology, 12 421-423, 1964).

Morphological observations were made in accordance with Shirling & Gottlieb (Shirling E.B. et al., International Journal of Systemic Bacteriology, 16, 313-340, 1966). The culture was grown at 28°C for 11 days on yeast extract, malt extract agar (YMA). The spore chain morphology was found to be of spiral/retina type, substrate mycelium was off-white and aerial mycelium was gray orange. Colonies are opaque, raised in the center with irregular edges, rough and hard in consistency.

Microscopic studies and cell wall analysis of the strain reveal that this strain belongs to the genus *Streptomyces*. However, the results show some stark differences between the new isolate and known FK-506 producers (Tables-1 and 2).

Cultural characteristics were observed on various kinds of solid media namely, oat meal agar, YMA, tap water agar, basal mineral agar, inorganic salt starch mineral agar, glycerol asparagine agar and Czapek agar. The culture was incubated at 28°C for 11 days. The culture exhibited very good growth on Czapek's agar, nutrient agar, potato dextrose agar and glucose asparagine agar. On basal mineral salt agar, tap water agar and oat meal agar the growth was sparse. Soluble pigment production was observed on YMA, in contrast to the Merck strain ATCC 55098, a known producer of FK-506. Coloration of vegetative mycelium of *Streptomyces glaucescens* MTCC 5115 ranges from white to off-white whereas in case of *Streptomyces tsukubaensis 9993*, another FK-506 producer strain, it ranges from pale pink to reddish orange to pale brown (Tables-1 and 2).

Biological & Physiological Properties of *Streptomyces glaucescens* MTCC 5115

The results are shown in Table-2. Melanoid pigment formation in *Streptomyces glaucescens* MTCC 5115 was positive whereas it was found to be negative in the earlier known producer of FK-506. Temperature range for growth on YMA was found to be 22-35°C, with an optimum at 28°C temperature.

The sugar utilization pattern of our isolate vis-à-vis known FK-506 producing strains showed ready utilization of fructose, galactose, Glucose, mannitol, sucrose; poor utilization of rhamnose and no utilization of arabinose, m-inositol, raffinose, salicin and xylose (Table-3).

Streptomyces glaucescens MTCC 5115 sparingly utilized phenylalanine and proline but readily utilized histidine.

TABLE 1

COMPARATIVE MORPHOLOGICAL AND CULTURAL PROPERTIES OF *Streptomyces glaucescens* MTCC 5115 WITH KNOWN FK-506 PRODUCERS

S.No.	Test	Strain		
		***Streptomyces glaucescens* MTCC 5115**	***Streptomyces tsukubaensis* ATCC 9993**	***Streptomyces species* ATCC 55098**
1	Cell wall aminoacids	LL-DAP	LL-DAP	LL-DAP
2	Cell wall sugars	No diagnostic sugars	Data not available	Glucose
3	Cell wall type	Type 1	Type 1	Type 1
4	Spore chain morphology	Spiral/Retina	Rectiflexibles	Straight chain
5	Aerial mycelium (YME 20 days)	Gray orange	Light gray	Yellowish white
6	Diffusible pigment	Pale yellow	Dull reddish orange	Negative
7	Diffusible pigment Produced	Positive	Positive	Negative
8	Colour series	Off white	Gray	White or yellow
9	Gram's reaction	Gram positive	Gram positive	Gram positive
10	Acid fast staining	Negative	Data not available	Data not available

TABLE 2

BIOLOGICAL AND PHYSIOLOGICAL CHARACTERISTICS OF *Streptomyces glaucescens* MTCC 5115

S.No.	Test	Strain		
		***Streptomyces glaucescens* MTCC 5115**	***Streptomyces tsukubaensis* ATCC 9993**	***Streptomyces species* ATCC 55098**
1	Melanin pigment	Positive	Positive	Negative
2	Nitrate reduction	Negative	Negative	Data not available
3	Growth on 7% NaCl	Negative	<=3%	Data not available
4	Xanthine	Positive	Data not available	Data not available
5	Optimum growth temperature	28°C	28°C	27°C

TABLE 3

SUGAR UTILIZATION PATTERN OF *Streptomyces glaucescens* MTCC 5115*

S.No.	Sugars	Strain		
		***Streptomyces glaucescens* MTCC 5115**	***Streptomyces tsukubaensis* ATCC 9993**	***Streptomyces species* ATCC 55098**
1	Arabinose	Negative	Negative	Poor positive
2	Fructose	Positive	Negative	Moderate utilization
3	Galactose	Positive	Negative	Data not available
4	Glucose	Positive	Doubtful	Moderate
5	Meso-Inositol	Negative	Negative	Negative
6	Mannitol	Positive	Negative	Poor utilization
7	Raffinose	Negative	Negative	Poor utilization
8	Rhamnose	Positive weak	Negative	Poor utilization
9	Salicin	Negative	Doubtful	Data not available
10	Sucrose	Positive	Doubtful	Negative
11	Xylose	Negative	Negative	Negative

* Pridham, T.G. and Gottlieb D.; The utilization of carbon compounds by some Actinomycetales as an aid for species determination. J. Bacteriology 56, 107-117, 1948.

Comparison of various morphological, biological and physiological characteristics showed that *Streptomyces glaucescens* MTCC 5115 is a different strain than the earlier known producers of FK-506. A comparison of restriction fragment analysis of 16s r DNA of *Streptomyces glaucescens* MTCC 5115 with known producers of FK-506 *(Streptomyces tsukubaensis 9993)* showed a clear cut difference thereby further confirming it to be a different strain.

Accordingly, a comparison of this strain was made with various *Streptomyces species* in light of the published description (Bergy's Manual of Determinative Bacteriology 8th edition, 1974). As a result of the comparison, the strain *Streptomyces glaucescens* MTCC 5115 is considered to have close resemblance to *Streptomyces glaucescens.*

Fermentation Methodology

FK-506 can be produced by culturing *Streptomyces glaucescens* MTCC 5115 strain in aqueous nutrient medium containing sources of assimilable carbon and nitrogen, preferably under submerged aerobic conditions. The aqueous medium is preferably maintained at a pH of about 6-8 till harvest.

The preferred sources of carbon in the nutrient medium are carbohydrates such as glucose, xylose, galactose, glycerol, starch, dextrin, maltose, soybean oil and the like. Other source may include rhamnose, raffinose, arabinose, mannose, salicin, sodium succinate, and the like.

The preferred sources of nitrogen are yeast extract, soy peptone, soybean meal, cotton seed meal, corn steep liquor, wheat peptone, maize gluten, milk powder and wheat germ and the like.

The carbon and nitrogen sources, though advantageously employed in combination, need not be used in their pure form.

In addition, mineral salts of calcium, magnesium, sodium, cobalt, copper and potassium can also be added to the medium. If necessary, especially when the culture medium foams seriously, a defoaming agent, such as liquid paraffin, fatty oil, plant oil, mineral oil or silicone may be added.

Furthermore, when growth is carried out in large tanks, preferably vegetative form of microorganism is used in order to avoid lag phase in the production of FK-506. Therefore it is

desirable first to produced vegetative form of the organism by inoculating medium with spores or mycelia of the organism from the slant and culturing said inoculated medium, also called the seed medium (stage I) and then transferring the stage I seed into II stage seed medium (stage II), this seed can be used for inoculating the production medium.

During fermentation the culture grows in the form of pellets and hence it requires low agitation to meet the oxygen demand of the culture. This provides an advantage over the other *Streptomyces species* which grow in the filamentous form. This often causes shortage of oxygen in the culture so in order to increase oxygen supply; agitation rate is increased which in turn further causes lot of shear of hyphae and activity of the microorganism tend to decrease.

The fermentation is conducted at a temperature between 20-40°C preferably at 24-28°C for a period of 5-15 days, which may vary according to fermentation conditions and scale.

The produced FK-506 can be detected from the cultural medium by conventional means, e.g. High Pressure Liquid chromatography (HPLC). The FK-506 substance produced is found in the cultured medium and filtrate, and accordingly can be isolated and purified from the mycelium and the filtrate, which are obtained by extraction with solvents like ethyl acetate, methanol, toluene and the like pH adjustment and treatment with absorbents used generally such as activated charcoal, silica gel, alumina or the like and treatment with resins like anion and cation resins to remove impurities.

FK506 is analyzed from the culture broth by HPLC.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1

Isolation of *Streptomyces glaucescens* MTCC 5115

Streptomyces glaucescens MTCC 5115 was isolated from soil by using dilution plate technique as described below.

Soil samples were collected from different geographical areas of India in order to isolate new microorganisms producing FK-506. The samples were air-dried and a pre-treatment was given to each sample by heating at 90°C for 1 hour. One gram of the pretreated sample was taken in a sterile test tube and volume was made up to 10 ml with sterile distilled water. The mixture was blended for 10 seconds and allowed to stand for 1 hour. Serial dilutions were made in pre-sterilized distilled water and plated on asparagine-Glycerol medium containing 50 μg/ml each of chloramphenicol and nystatin/cycloheximide. One ml suspension was used for plating. The plates were incubated at 28°C for 7-10 days.

Isolated colonies were picked up on fresh YMA plates. The plates were incubated at 28°C for 10 days. The growth on the plates was picked up on YMA slants and cultured for 10-11 days at 28°C. These slants were stored for further use.

Example 2

Screening of the isolates:

A spore/mycelial suspension of each isolate were prepared with 2.5 ml of 0.85% sodium chloride solution obtained from 11 day old YMA slant. The suspension was used to inoculate 35 ml of sterile KE seed medium (US Patent No.5,194,378).

The pH of the seed medium was adjusted to 6.9 before sterilization. The culture was incubated for 44-48 hours on a rotary shaker at 28°C, then 2 ml of the seed culture was used to inoculate 25 ml of FKA production medium and the fermentation was carried out as per the conditions described in US Patent No. 5,194,378.

Methanol extracts of the fermentation broths were tested for antifungal activity against a mutant strain of *Aspergillus terreus* using FK-506 as standard. Twenty two strains showed a clearing zone thereby showing antifungal activity against *Aspergillus terreus*. Extracts of these strains were confirmed for the presence of FK-506 using HPLC. One of the strains, *Streptomyces glaucescens* MTCC 5115, showed a very small peak at the same retention time as that of the standard FK-506. To confirm it to be actually the FK-506 product peak, a new media / improved process was designed for the same as described in Example 4.

Example 3

Restriction fragment analysis of 16s rDNA

A comparison of restriction fragment pattern of 16s rDNA between *Streptomyces glaucescens* MTCC 5115 and *Streptomyces tsukubaensis 9993* was made using different restriction endonucleases (BamH1, Bgl1, Nco1, Sma1, EcoR1, HindIII, EcoRV, Stu1 & Psn AI). These experiments reveal that *Streptomyces glaucescens* MTCC 5115 exhibits a different prototype.

Example 4

Process optimization:

A spore/mycelial suspension of *Streptomyces glaucescens* MTCC 5115 strain was prepared with 2.5 ml of 0.85% sodium chloride solution obtained from 11 day old YMA slant. The seed was grown through Stage I / II for 44-48 hours at 28°C.The composition of the seed medium is given below.

Seed medium	
Ingredients	**g per litre**
Dextrin	10.0
Dextrose	1.0
Cotton seed meal	2.5
Yeast extract	5.0
Casein enzyme hydrolysate	5.0
$MgSO_4.7H_2O$	0.05
Milk powder	2.0
Phosphate buffer (0.67M) pH 7.0	2 mL
NaCl	0.5
$ZnSO_4.7H_2O$	0.001
$MnSO_4.4H_2O$	0.005
$CaCl_2$	0.02
$FeSO_4.5H_2O$	0.025

Two ml of seed culture was used to inoculate production medium having the following composition.

Production medium	
Ingredients	**g per litre**
Dextrose	5.0
Dextrin	120.0
Cotton seed meal	10.0
Soya bean meal	10.0
Soya peptone	10.0
Glycerol	10.0
KH_2PO_4	0.8
CaCO3	1.5
Polyethylene glycol	1.0

The pH of the nutritive medium was adjusted to 7.0-7.2 before sterilization and the medium was sterilized at 121°C for 25 minutes.

The fermentation was carried out for 290-310 hours at 240 rpm, 24°C and analyzed for FK-506 by HPLC. The FK-506 peak was very distinct and clear.

Spiking of this HPLC peak using FK-506 working standard confirmed the presence of FK-506 product in the broth. The highest titer of FK-506 was 5-10 µg/ml after about 300 hours from above mentioned production medium.

Example 5

Isolation and Purification of FK-506:

Six liters of fermentation broth was acidified to pH 4.0, and it was extracted twice with equal volume of ethyl acetate. The ethyl acetate layer was pooled (6 liters) and concentrated to 100 ml at 40°C under vacuum. This was further purified by known techniques of column chromatography and the isolated product was tested for MASS by LCMS.

The analytical results demonstrated that the compound isolated was similar to Fujisawa's FR-900506 (FK-506) as described in European Patent No. 184162 and US Patent No. 4,894,366.

Dated this 17TH day of **October, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

1284 DEL 03

ABSTRACT

17 OCT 2003

PRODUCTION OF TACROLIMUS (FK-506) USING NEW STREPTOMYCES SPECIES

The present invention relates to a process for the production of immunosuppressant agent, tacrolimus (FK-506) utilizing the new microorganism *Streptomyces glaucescens* MTCC 5115.

Ranbaxy Laboratories Limited

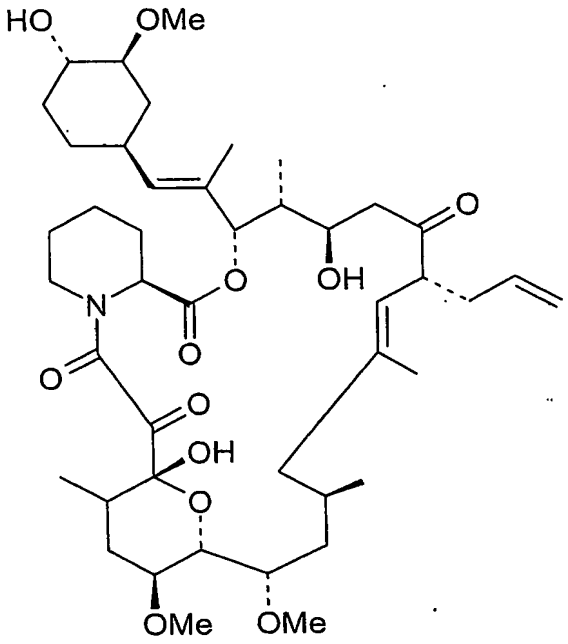
No. of sheets = 01

Application No.

Sheet 01 of 01

DEL 07

17 OCT 2003



FORMULA I

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)

Company Secretary

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☑ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☑ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.